WILLIAM T. KEETON
CORNELL UNIVERSITY

JAMES L. GOULD
PRINCETON UNIVERSITY

WITH CAROL GRANT GOULD

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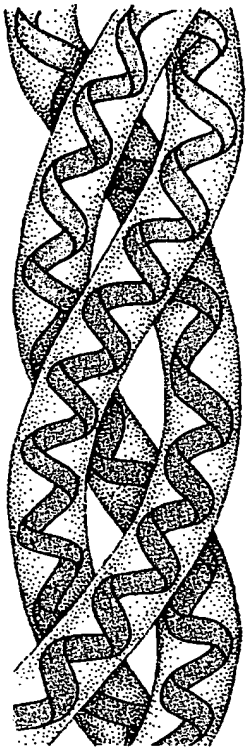


3.23 Model of a portion of a molecule of collagen Three polypeptide chains, each helically coiled, are wound around one another to form a triple helix. The "sheaths" here and in Figures 3.24 and 3.25 are intended as a reminder that each molecule consists not merely of a backbone, but also of R groups, which give it volume.

most abundant protein in higher vertebrates. This is ***collagen***, which may constitute one-third or more of all the body protein; it is especially abundant in skin, tendons, ligaments, and bones, and in the cornea of the eye. A molecule of collagen is composed of three polypeptide chains, each first helically coiled and then wound around the other two to form a triple helix (Fig. 3.23). What facilitates the intertwining of the three chains is that every third amino acid in the chains is glycine, whose R group, being only a single hydrogen atom (Fig. 3.16), takes up very little room. The chains are held together by hydrogen bonds. Collagen fibers are exceedingly strong and very resistant to stretching.

Far more complex in spatial conformation than the fibrous proteins are the globular proteins, whose polypeptide chains are folded into complicated spherical or globular shapes (Fig. 3.24). Because of charged and polar R groups on their exposed surfaces, globular proteins, which include enzymes, proteinaceous hormones, antibodies, and most blood proteins, are usually water-soluble. Typically, they are made up of sections of α helix interspersed with nonhelical regions; some globular proteins, however, have no obvious secondary structure at all. The protein myoglobin, which is the oxygen-storage protein in muscles, provides a more typical example. It consists of one polypeptide chain containing eight major sections of secondary structure—α helices—connected by short regions of irregular (nonhelical) coiling. At each nonhelical region, the three-dimensional orientation of the polypeptide chain changes, giving rise to the protein's characteristic folding pattern. This three-dimensional folding pattern, which is superimposed on the secondary structure, is called ***tertiary structure***. In practice, tertiary structure is difficult to determine. The protein must first be crystallized. Then X rays are beamed through the crystals; deflected by the electrons of the thousands of atoms, they form a pattern which is then deciphered by a computer.

When a globular protein is composed of two or more independently folded polypeptide chains loosely held together, usually by weak bonds, the manner in which the already folded subunits fit together is called ***quaternary structure*** (Fig. 3.25).

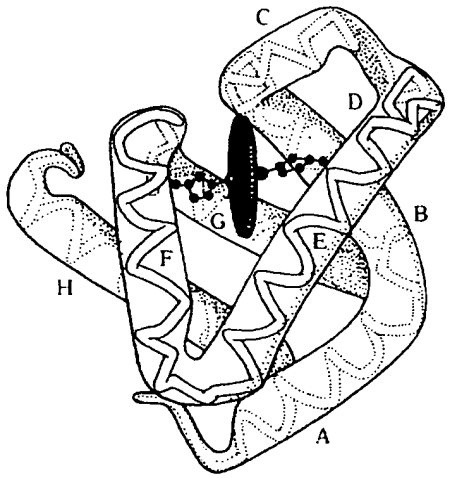
Several aspects of a protein's primary structure (that is, its amino acid sequence) contribute to producing its tertiary and quaternary structure. If, for example, a polypeptide chain contains two cysteine units, the intrachain disulfide bond joining them may introduce a fold in the chain or stabilize one created in other ways (Fig. 3.19). The most common source of folding is proline. Wherever there is a proline, a kink or bend occurs, because the structure of proline is such that it cannot conform to the geometry of an α helix; as we have seen, proline, though one of the building-block units of protein, is not technically a true amino acid, since its R group circles around and links with its amino group (Fig. 3.16). Four of the eight bends in globular myoglobin, in fact, result from the presence of prolines in the chain.

The distinctive properties of the various R groups of the amino acids also impose constraints on the shape of the protein. For example, hydrophobic groups tend to be close to each other in the interior of the folded chains—as far away as possible from the water that suffuses living tissue—whereas hydrophilic groups tend to be on the outside, in contact with the water. Pola

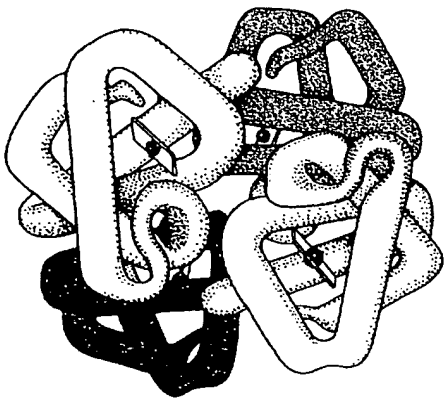
R groups, such as that of tyrosine (Fig. 3.16), tend to assume positions where they can form hydrogen bonds with other polar R groups; similarly, electrically charged R groups can form ionic bonds with oppositely charged groups (aspartic acid and lysine, for example, form an ionic bond when they are forced into the interior of the protein). In myoglobin, again, all the hydrophobic peptides are in the interior, and all but two of the hydrophilic peptides are on the outside. (The two exceptions, both ionic amino acids, hold the heme group in place.) Thus the various kinds of weak bonds discussed earlier play crucially important roles in forming and stabilizing the tertiary structure of proteins.

As this discussion suggests, there are compelling reasons to believe that the primary structure of a protein determines its spatial conformation. More specifically, it appears that the primary structure determines the energetically most favorable, and therefore most stable, possible arrangement of the polypeptide chains. Hence the question, long perplexing to biochemists, of how conformation is specified when a protein is being synthesized becomes synonymous with the question of how amino acid sequence is specified—a question no longer so perplexing to scientists, as we shall see in a later chapter.

Further support for the idea that primary structure determines conformation comes from studies of ***denatured*** proteins—proteins that have lost most of their secondary, tertiary, and quaternary structure, and with it their normal biological activity, through exposure to high temperature or extreme pH. That a denatured protein should lack the characteristic biological activity of the natural protein is an indication that its conformation is functionally essential. Since conformation is dependent in large part on weak bonds (which are very sensitive to temperature and pH), it is easily disrupted by anything that breaks or alters those bonds; it is stable only within a limited range of temperature and pH. Even brief exposure to high temperatures (usually above 60°C) or to extremes of pH will cause denaturation of most globular proteins. But under favorable test-tube conditions some denatured proteins can spontaneously regain their native three-dimensional conformation; they can refold, and recover their normal biological activity. Since only the primary structure is available to dictate



3.24 Spatial conformation of a molecule of myoglobin
Myoglobin, a globular protein related to hemoglobin and, like hemoglobin, characterized by a strong affinity for molecular oxygen, is a single complexly folded polypeptide chain of 151 amino acid units; attached to the chain is a nonproteinaceous "prosthetic" group called heme (represented by the disc). The polypeptide chain consists of eight sections of α helix (labeled A through H), with nonhelical regions between them. These nonhelical regions are a major factor in determining the tertiary structure of the molecule—that is, the way the helical sections are folded together. (Section D cannot be seen in this drawing, because it is oriented perpendicular to the plane of the page.)



3.25 Quaternary structure of hemoglobin
A single molecule of hemoglobin is composed of four independent polypeptide chains, each of which has a globular conformation and its own prosthetic group. The spatial relationship between these four—the way they fit together—is called the quaternary structure of the protein.